**A family of helminth-derived TGF-β mimics provide key insights to Treg and innate immune cell activation.**

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Helminth parasites have evolved sophisticated methods for manipulating the host immune response to benefit their long-term survival and circumvent therapeutic interventions. A pivotal mechanism for dampening protective immunity is through the secretion of immunomodulatory proteins. Studies on the secreted products of *Heligmosomoides polygyrus* have identified a novel mimic of TGF-β (TGM-1), organised as a 5-domain modular protein. *In vitro,* TGM-1 induces the differentiation of murine and human Foxp3+ T regulatory (Treg) cells via signalling through the canonical TGF-β receptor/SMAD pathway in both murine and human T cells, despite sharing no structural homology to any member of the TGF-β family. Treg induction requires domains 1-3, while domains 4 and 5 increase the potency of the mimic through binding to co-receptors. Nine additional proteins with significant sequence similarity to TGM-1 are also found in the secretomes of adult (TGMs 2-6) and larval (TGMs 7-10) life stages. These TGM family members display contrasting abilities to induce or inhibit Treg cell induction *in vitro,* vary in TGF-β signalling in different cell types, and induce markedly disparate surface expression of key activation markers, including CD39, CD103 and PD-L1. Recently, through co-precipitation, followed by mass spectrometry, a novel co-receptor for TGM-1 has been identified as CD44, a cell surface marker found on many cell types, including effector T cells and macrophages, which is involved in the sensing of hyaluronan upon cellular damage. Therefore, *H. polygyrus* has evolved to secrete TGM-1 to act preferentially on cells which specifically co-express TGF-β receptors and CD44. Indeed, T cells from CD44 knockout mice have a significantly impaired ability to induce Treg cells in response to TGM-1, but have no such impairment in response to TGF-β. We have now identified several additional co-receptors and signalling pathways for each TGM which account for the cell-specific effects of each family member. In addition to Treg cell induction, *in vitro* stimulation of macrophages with certain TGMs induces an anti-inflammatory state, suppressing secretion of pro-inflammatory cytokines in response to LPS co-stimulation. Understanding these variances will provide key insights to helminth immunomodulation, including the identification of latent co-receptors as well as novel co-stimulatory and signalling pathways that may provide unique targets for drug discovery.